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Blood Pressure in 6-Year-Old Children Born Extremely Preterm

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***Background*—**Advances in perinatal medicine have increased infant survival after very preterm birth. Although this progress is welcome, there is increasing concern that preterm birth is an emerging risk factor for hypertension at young age, with implications for the lifetime risk of cardiovascular disease.

***Methods and Results*—**We measured casual blood pressures (BPs) in a population-based cohort of 6-year-old survivors of extremely preterm birth (<27 gestational weeks; n=171) and in age- and sex-matched controls born at term (n=172). Measured BP did not differ, but sex, age-, and height-adjusted median *z* scores were 0.14 SD higher (*P*=0.02) for systolic BP and 0.10 SD higher (*P*=0.01) for diastolic BP in children born extremely preterm than in controls. Among children born extremely preterm, shorter gestation, higher body mass index, and higher heart rate at follow-up were all independently associated with higher BP at 6 years of age, whereas preeclampsia, smoking in pregnancy, neonatal morbidity, and perinatal corticosteroid therapy were not. In multivariate regression analyses, systolic BP decreased by 0.10 SD (*P*=0.08) and diastolic BP by 0.09 SD (*P*=0.02) for each week-longer gestation.

Conclusions*—**Six-year-old children born extremely preterm have normal but slightly higher BP than their peers born at term. Although this finding is reassuring for children born preterm and their families, follow-up at older age is warranted. (J Am Heart Assoc.* **2017;6:e005858. DOI: 10.1161/JAHA.117.005858.)**

Key Words: follow-up study • hypertension • pediatrics • preterm birth

Preterm birth (<37 gestational weeks) complicates 1 in 10 pregnancies worldwide.[1,2] Countries where neonatal intensive care is accessible have had large increases in survival over past decades, including among extremely preterm infants (<28 weeks). In the early 1970s, 80% died during the first month of life, and survivors faced high risks of severe morbidity. Today, survival is 70% to 80%, and a majority of these infants are free from disability in later life.[3–6]

There are indications that development of the cardiovascular, renal, and autonomic nervous systems may be affected by preterm birth,[7–12] and risks of stroke and death from cardiovascular disease are increased in some[13,14] but not all[15] cohorts of adults who were born preterm. Earlier studies showed that blood pressure (BP) is already elevated in adolescence and adulthood after preterm birth.[16–18] Data from survivors in more recent cohorts of extremely preterm infants are scarce.[11,19]

Continued studies of BP development after extremely preterm birth are important because survivors today are even more immature[20] and have health outcomes that may be poorer than those of their peers born later in pregnancy.[13,18,21] The potentially more vulnerable cardiovascular and renal systems of infants born extremely preterm could also be more susceptible to altered developmental trajectories, with long-standing BP elevation already starting in early childhood.

We previously showed an increased risk of elevated and hypertensive BP at 2.5 years of age in a regional cohort of survivors of extremely preterm birth.[22] Hypothesizing that this risk of elevated BP persists into school age, we extended this follow-up study to half of Sweden. We investigated BP at

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Clinical Perspective

What Is New?

- In a population-based cohort study of 6-year-old children born at 22 to 26 weeks of gestation, we show that participants born extremely preterm have higher blood pressures than controls born at term, but their blood pressure levels are normal.

What Are the Clinical Implications?

- Although our findings are reassuring for the growing population of children born at the limits of viability, we recommend that blood pressure is measured in children and adults born preterm at every health visit for early detection of developing hypertension.

6.5 years of age in a prospective population-based cohort of survivors of preterm birth at <27 gestational weeks who were born in 2004–2007. In addition to comparing BPs of children born extremely preterm with those of children born at term, our aim was to evaluate effect size, sex differences, and any dose-response relationship with gestational age and contributions from other perinatal risk factors.

Methods

Participants

EXPRESS (Extremely Preterm Infants in Sweden Study) included all pregnant women residing in Sweden and delivering infants before 27 weeks of gestation from April 1, 2004, to March 31, 2007. Detailed characteristics of this prospectively collected population-based cohort and data on survival,[3] neonatal morbidity,[23] and neurodevelopmental[6] and vascular outcomes[12] were reported previously.

All EXPRESS children were invited to a comprehensive follow-up study at age 6.5 years ±3 months. Of the 7 regions engaged, 3 regions—Lund, Stockholm, and Umeå—conducted cardiovascular and lung function assessments including BP measurements, in addition to neurodevelopmental testing. Of the 494 survivors in the EXPRESS cohort, 262 (51%) were from these 3 regions.

Exclusion criteria were congenital cardiovascular or pulmonary malformations or ongoing cardiovascular or lung disease at assessment age. A flow chart of inclusions and exclusions is shown in Figure. There were no significant differences between those participating in the study and those lost to follow-up regarding mean gestational age at birth (25.4 versus 25.3 weeks, P=0.13), mean birth weight (785 versus 769 g, P=0.15), or sex distribution (45% versus 50% female, P=0.39). We did not have access to any data at 6.5 years of age for those lost to follow-up.

Using the Swedish Medical Birth Register held at the National Board of Health and Welfare, each child born preterm was matched with a healthy control child born at term (control) and with the same sex, date of birth, hospital, residency, and mother's country of birth. A pool of 10 controls for each preterm participant was randomly selected from the Swedish Medical Birth Register. Invitations were sent until 1 control child for each preterm child agreed to participate. If all invited control candidates declined and the list of eligible children was depleted, the controls were listed as missing (n=4; see figure 1 in Mohlkert et al[12]).

BP Measurements

Standard operating procedures were used for BP measurements. The participating child and family were asked before arrival not to reveal their assigned experimental group to the research nurses, who were blinded. Families were scheduled to attend in the morning. Each participant's medical history, parents' smoking status, and medical history including family history of cerebrovascular stroke, myocardial infarction, and coronary bypass surgery in parents or grandparents were obtained using a questionnaire.

At arrival, height and weight as well as head and waist circumferences were measured with the child undressed to light clothing without shoes. Body mass index (BMI) was calculated as weight in kilograms divided by height in square meters, and body surface area was calculated according to Haycock.[24]

After 15 minutes of calm adaptation to the investigation room and while the children were seated in a chair or a parent's lap, a validated oscillometric device (Omron HEM 907; Omron Healthcare, Kyoto, Japan) was used to measure systolic BP (SBP) and diastolic BP (DBP) and heart rate in the right arm with an appropriate cuff size covering two-thirds of the upper arm. Three consecutive measurements were obtained in 329 of 343 participants (96%); it was possible to measure BP twice in 8 of 343 (2.3%) and once in 6 of 343 (1.7%). No BP measurement was obtained in 5 participants (all preterm), and they were excluded from the analyses. Measurements were taken with at least 2-minutes intervals, without turning the machine off between the measurements, and mean values were calculated. In addition to the 343 of 348 children with at least 1 BP recorded, heart rate was measured in 341, and they were included in the analyses.

SBP and DBP z scores were calculated using age-, sex-, and height-adjusted BP nomograms for children.[25] Age- and sex-adjusted z scores for current height were calculated in STATA using the World Health Organization growth reference data from 2007 for ages 5 to 19 years (http://www.who.int/growthref/en/).

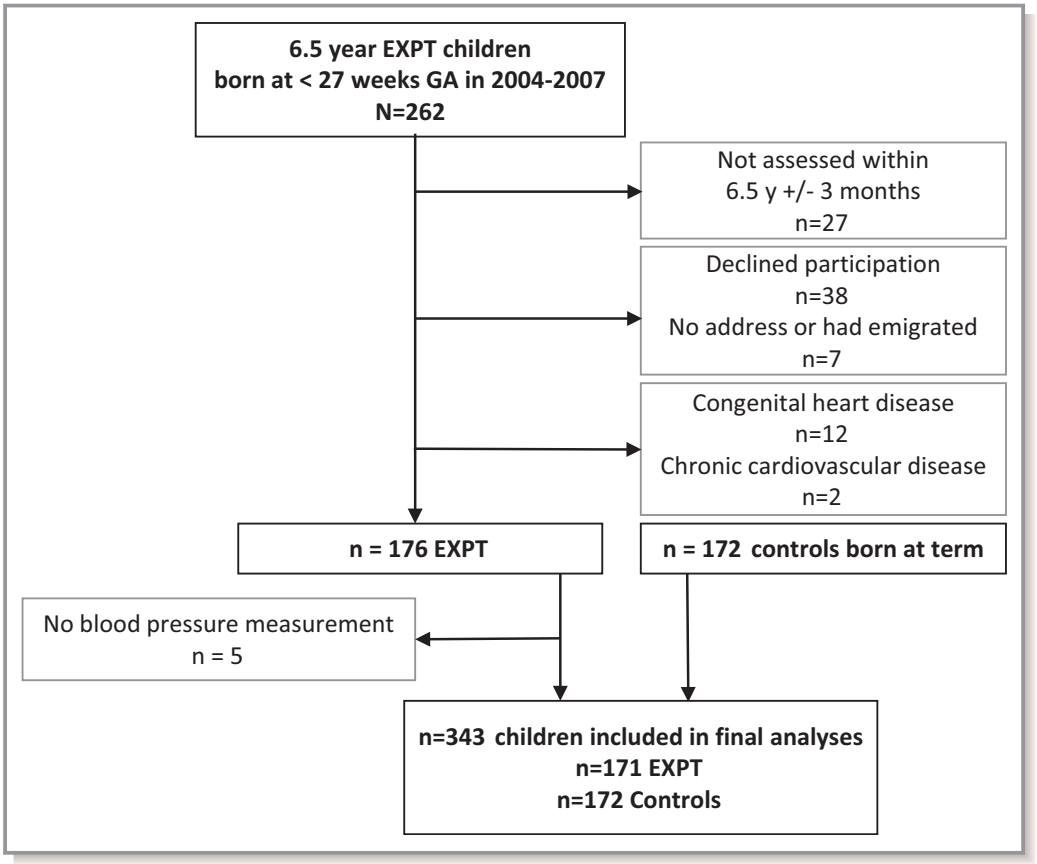

Figure. Flow chart of inclusions and exclusions in the study. EXPT indicates extremely preterm group; GA, gestational age.

The EXPRESS cohort register provided maternal and perinatal data.[3,23] EXPRESS was approved by the Regional Ethics Review Board in Lund (no. 42/2004), and approval for the follow-up study was obtained from the Regional Ethics Review Board in Stockholm (no. 2010/520-31/2 and amendment no. 2011/376-32). All parents and children invited to participate received oral and written information, and the parents or legal guardians of participating children signed informed consent. Follow-up ended in January 2014.

Statistical Methods

The distribution of continuous variables was assessed with the Shapiro-Wilk test. DBPs and heart rate were not normally distributed; therefore, the Mann–Whitney *U* test was used to test for group differences between children born extremely preterm and controls. The Pearson χ^2 test was used to test for group differences in proportions; when numbers were <10, the Fisher exact test was used.

For examining determinants of BP in the whole sample (n=343), we used linear stepwise regression with backward selection of the following covariates: extremely preterm/term status, heart rate, BMI, sex, maternal education, and maternal smoking in pregnancy, using a *P* value cutoff of 0.15 for inclusion in the model. In the final regression models, possible clustering of data was taken into account by using a mixed-effects linear model (mixed in STATA) with examination center (Stockholm, Lund, and Umeå) as the random-effects variable. For each group—extremely preterm (EXPT) and control (CTRL)—we also calculated and compared the proportions of children with SBP or DBP in the hypertensive range defined as BP >90th percentile for age, height, and sex.[25]

Within the EXPT group (n=171), the determinants of BP were investigated in the same way. We explored maternal factors (education, maternal age, parity, smoking during pregnancy), obstetric factors (antenatal corticosteroids, preeclampsia, and placental abruption), and infant factors: small for gestational age (defined as a birth weight <2 SD below the mean birth weight for gestational age and sex according to intrauterine growth curves[26]), multiple birth, systemic postnatal corticosteroids, bronchopulmonary dysplasia (defined as need for oxygen with a fraction of inspired oxygen of >30% or need for respiratory support [mechanical ventilation or nasal continuous positive airway pressure] at 36 weeks of postmenstrual age), treated patent ductus arteriosus, retinopathy of prematurity stage ≥3,

intraventricular hemorrhage grade ≥3, and cystic periventricular leukomalacia. Covariates with $P<0.15$ for either SBP or DBP z scores in the EXPT group were entered into a stepwise model together with BMI, sex, and heart rate. The final model included gestational length, small for gestational age status, and the child's sex, BMI and heart rate at follow-up and was analyzed in a mixed-effects linear model with SBP or DBP z scores as dependent variables and examination center as the random-effects variable. The sample size permitted 80% power to detect an estimated difference in SBP of 0.3 SD.

Results

Maternal, obstetric, and infant characteristics of the 2 groups are presented in Table 1. The proportion of EXPT-group mothers who had university education was lower compared with CTRL-group mothers, and the proportion of EXPT-group mothers who smoked during pregnancy was higher, although low in both groups. There was no difference in family history of cardiovascular disease between the groups (Table 1).

At 6.5 years of age, children in the EXPT group were significantly lighter and shorter and had lower BMI than those in the CTRL group (Table 2). Crude SBP and DBP did not differ between the 2 groups, but after taking height into account, z scores for both SBP and DBP were higher in the EXPT group than in the CTRL group (Table 3). When restricting the analyses to BP measurements 2 and 3 in the 329 participants who had all 3 measurements, the median SBP z scores were 0.09 ((interquartile range [IQR]): −0.34 to 0.59) in the EXPT group and −0.07 (IQR: −0.57 to 0.40) in the CTRL group (P=0.026). The corresponding DBP z scores were −0.06 (IQR: −0.41 to 0.28) for EXPT and −0.29 (IQR: −0.71 to 0.21) for CTRL (P=0.002). Resting heart rate was higher for EXPT than CTRL participants (Table 3).

After stratification by sex, group differences in SBP and DBP z scores and in heart rate were confined to boys, whereas girls in the EXPT group did not exhibit any statistically significant differences in BP or heart rate compared with girls born at term (Table 4). However, CTRL girls had higher SBP z scores than CTRL boys (P=0.002; Table 4), and DBP z scores were higher for both EXPT and CTRL girls compared with EXPT and CTRL boys (P=0.02 for comparison between EXPT girls and boys, and P=0.005 for comparison between CTRL girls and boys; Table 4).

Using a P-value cutoff of 0.15 for inclusion in the final regression model, maternal education and smoking in pregnancy were excluded (P=0.51 and P=0.85, respectively). In the final multivariate regression analyses with SBP or DBP as dependent outcomes, the adjusted regression coefficients for being born extremely preterm compared with at term were of the same magnitude as the regression coefficients for 10-bpm higher heart rate, or ≈2 to 4 times higher than the effect on SBP or DBP from a 1-U increase in BMI (Table 5).

Within the EXPT group, we found no significant associations of maternal education, smoking in pregnancy, preeclampsia, use of antenatal or postnatal corticosteroids, or neonatal morbidity with BP at 6.5 years of age. In the final regression model, shorter gestation, higher heart rate, and higher BMI at follow-up were independently associated with SBP or DBP (Table 6). For each week-longer gestation, SBP (P=0.08) and DBP (P=0.02) decreased by ≈0.1 SD in children born extremely preterm.

Table 1. Maternal and Neonatal Characteristics of 6.5-Year-Old Children Born Extremely Preterm and at Term

	EXPT (n=171)	CTRL (n=172)	*P* Value
Maternal data			
Age, y (SD)	31.4 (5.5)	31.7 (4.6)	0.58
University education	79 (46.5)	104 (60.5)	0.008
Smoking in pregnancy	9 (5.3)	2 (1.2)	0.04
Obstetric data			
Multiple pregnancy	32 (18.7)	0	N/A
Preeclampsia/ eclampsia	15 (8.8)	0	N/A
Placental abruption	18 (10.5)	0	N/A
Antenatal corticosteroid treatment	144/155 (92.9)	0	N/A
Infant data			
Family history of CVD*	77/163 (47.5)	64/157 (40.8)	0.24
Gestational length in weeks			
Mean (SD)	25.4 (1.0)	39.8 (1.2)	N/A
Range	22.9–26.9	37.1–41.9	
Birth weight, g			
Mean (SD)	786 (169)	3595 (465)	N/A
Range	348–1161	2430–4985	
Small for gestational age, n (%)	22 (12.9)	3 (1.74)	<0.001
Large for gestational age, n (%)	7 (4.6)	8 (4.1)	0.8
Major neonatal morbidity†	85 (49.7)	0	N/A

Data are n (%) if not stated otherwise. CTRL indicates control group (children born at term); CVD, cardiovascular disease; EXPT, extremely preterm group; N/A, not applicable.
*Stroke, myocardial infarction, or coronary artery bypass grafting surgery in parent or grandparent.
†Major neonatal morbidity: retinopathy of prematurity stage ≥3, severe bronchopulmonary dysplasia (defined as need for oxygen with a fraction of inspired oxygen of >30% or need for respiratory support [mechanical ventilation or nasal continuous positive airway pressure] at 36 weeks of postmenstrual age), necrotizing enterocolitis, intraventricular hemorrhage grade ≥3, or periventricular leukomalacia.

Table 2. Anthropometry of 6.5-Year-Old Children Born Extremely Preterm and at Term

	EXPT (n=171)	CTRL (n=172)	*P* Value
Girls, n (%)	76 (44.4)	73 (42.7)	0.78
Age, y	6.6 (0.19)	6.7 (0.18)	0.27
Weight, kg	20.6 (3.7)	24.2 (4.1)	<0.001
Height, cm	118 (5.6)	123 (4.9)	<0.001
BMI, kg/m^2	14.7 (1.7)	16.0 (2.1)	<0.001
Weight, *z* score*	−0.54 (1.2)	0.60 (1.0)	<0.001
Height, *z* score*	−0.21 (1.0)	0.70 (0.91)	<0.001
BMI, *z* score*	−0.62 (1.1)	0.22 (1.2)	<0.001
Head circumference, cm	51.2 (2.0)	52.7 (1.6)	<0.001
Waist circumference, cm	54.5 (6.6)	57.2 (5.2)	<0.001

BMI indicates body mass index; CTRL, control group (children born at term); EXPT, extremely preterm group.
*Based on World Health Organization growth reference data (http://www.who.int/growthref/en/).

Discussion

We report that 6.5-year-old children who were born extremely preterm have higher SBP and DBP than children born at term, that DBP was ≈0.1 SD lower for every 1-week increase in gestational age, and that perinatal morbidity was not associated with BP at 6.5 years of age. In addition, office heart rate was 3 bpm higher in children born extremely preterm than in children born at term.

Part of this population-based cohort (68 survivors of extremely preterm birth) had BP measured at 2.5 years of age.[22] Because of small numbers and differential follow-up (among both index and control participants) at 6 years of age, we refrained from statistical testing of our longitudinal data. We note, however, that group differences in BP were already present at 2.5 years of age.[22]

We found slightly higher BP in children born extremely preterm. Because tracking of BP from childhood to adulthood has been reported to be strong,[27,28] a small difference in early childhood may become larger later in life. In a previous population-based cohort study, BP at 6 and 11 years of age did not differ between those born extremely preterm or at term.[19,29] In adolescence and at young adult age, however, several studies including a systematic review reported up to 2- to 4-mm Hg higher SBP and DBP in people who were born preterm.[7,11,16,18,30–32] Although this increase in BP may seem small at an individual level, increasing the mean BP in a population by 2 to 5 mm Hg may have significant effects on the numbers who will have hypertension[33] and later stroke or ischemic heart disease.[34–36] Given that a dose-response relationship exists with gestational age[18,32,33] and that the association between preterm birth and elevated BP has been found to be independent of shared familial factors[18] and intrauterine growth restriction,[30,31,37] there may be a causal relationship.

The mechanisms by which BP levels or control appear to be compromised in children and young adults who were born preterm are not yet fully understood. Possible contributing factors include impaired morphological development of glomeruli and fewer nephrons on the basis of interrupted kidney development resulting in smaller kidneys,[9,38] microvascular growth arrest and rarefaction building up peripheral vascular resistance,[7,39,40] and sympathoadrenal overactivity.[8,41] As long as the underlying mechanisms remain ambiguous, early interventions will be difficult to design. Interestingly, preterm infants randomized to breast milk instead of formula had significantly lower BP at follow-up 16 years after the intervention,[42] indicating that early nutritional factors may play a role.

In our cohort, follow-up at 2.5[22] and 6 years of age showed larger BP elevation in boys born extremely preterm than in girls compared with their same-sex controls. Whether or not

Table 3. SBP, DBP, and Heart Rate in 6.5-Year-Old Children Born Extremely Preterm or at Term

	EXPT (n=171)	CTRL (n=172)	*P* Value
SBP, mm Hg	97.7 (92.7–103.0)	97.2 (93.5–103.3)	0.81
DBP, mm Hg	56.0 (52.3–60.3)	55.7 (51.3–60.3)	0.30
SBP, *z* score*	0.08 (−0.28 to 0.66)	−0.06 (−0.50 to 0.39)	0.02
DBP, *z* score*	−0.08 (−0.37 to 0.33)	−0.18 (−0.63 to 0.25)	0.01
SBP >90th percentile, n (%)	11 (6.5)	14 (8.1)	0.56
DBP >90th percentile, n (%)	6 (3.6)	1 (0.6)	0.06
Heart rate, bpm	88.2 (80–95.7)	85.0 (78.3–90.3)	0.005

Data are median (interquartile range) or n (%). CTRL indicates control group (children born at term); DBP, diastolic blood pressure; EXPT, extremely preterm group; SBP, systolic blood pressure.
*According to pediatric blood pressure nomograms by age, sex and height.[25]

Table 4. SBP, DBP, and Heart Rate in 6.5-Year-Old Children Born Extremely Preterm and at Term, Stratified by Sex

	Boys			Girls		
	EXPT (n=95)	CTRL (n=99)	*P* Value	EXPT (n=76)	CTRL (n=73)	*P* Value
SBP, mm Hg	97.3 (92.3–102)	96.7 (92.7–102.3)	0.75	97.7 (92.8–103)	98.0 (94.7–104.0)	0.43
DBP, mm Hg	55.3 (52.0–58.3)	54.3 (50.0–59.3)	0.33	58.0 (54.3–62.7)	57.7 (53.0–63.0)	0.56
SBP *z* score*	0.06 (−0.30 to 0.54)	−0.25 (−0.62 to 0.25)	0.005	0.19 (−0.27 to 0.68)	0.13 (−0.17 to 0.68)	0.83
DBP *z* score*	−0.13 (−0.42 to 0.10)	−0.37 (−0.68 to 0.17)	0.02	0.13 (−0.31 to −0.51)	−0.09 (−0.44 to 0.46)	0.16
SBP >90th percentile, n (%)	6 (6.4)	7 (7.1)	1.00	5 (6.6)	7 (9.6)	0.56
DBP >90th percentile, n (%)	4 (4.3)	1 (1.0)	0.20	2 (2.7)	0 (0)	0.50
Heart rate, bpm	87.3 (76.0–94.3)	83.7 (75.7–89.0)	0.04	88.3 (81.3–92.0)	86.7 (82.6–97.0)	0.06

CTRL indicates control; DBP, diastolic blood pressure; EXPT, extremely preterm group; SBP, systolic blood pressure.
*According to pediatric blood pressure nomograms by age, sex and height.[25]

this is a legacy of increased neonatal morbidity in boys born extremely preterm[43] or relates to other early sex differences remains to be clarified. Supporting the latter is the fact that CTRL girls had higher SBP and DBP *z* scores than CTRL boys, and EXPT girls had higher DBP *z* scores than EXPT boys. Follow-up in adolescence and adult life after preterm birth has shown elevated BP in those born extremely preterm, without any sex differences.[11,31]

Our data could not confirm that being small for gestational age at birth is a perinatal risk factor for high BP in children born extremely preterm. Over a life-course perspective, being born small for gestational age has been considered to be more harmful in terms of risk of hypertension than preterm birth.[44,45] However, life-course studies of historic perinatal cohorts may be biased by selective survival among those born preterm and do not contain today's survivors born after extremely short gestations. Our present and previous[18] results indicate that in addition to being born preterm, being small for gestational age at birth (ie, showing signs of fetal growth restriction) is not an added perinatal risk factor for high BP in follow-up of participants born preterm.

Perinatal risk factors such as antenatal corticosteroid therapy and severe neonatal morbidity were not associated with BP at 6 years of age. The long-term safety of antenatal corticosteroid therapy regarding BP was documented previously.[46] The lack of an association between severe neonatal morbidity and later BP also indicates that increased BP after preterm birth may reflect a developmental origin rather than the end result of strikes from perinatal morbidity.

The strengths of our study include the population-based and controlled design. The control group was chosen to avoid selection bias, and we note that the BPs in our control group are similar to those in a recently published normative BP standard for Swedish children.[47] Gestational age was estimated by ultrasound in practically all pregnancies, limiting the risk of misclassification. The follow-up time was 6 years, and we enrolled a comparatively large number of childhood survivors after birth at 22 to 26 weeks of gestation. BPs were measured in a standardized way, and the research nurse was blinded to group assignments. BP *z* scores were calculated according to established BP nomograms for use in children. Although the follow-up rate was 70%, dropout analysis did not indicate any selection bias.

Table 5. Determinants of SBP and DBP *z* Scores in 6.5-Year-Old Children Born Extremely Preterm or at Term (n=343)

	SBP *z* Score	*P* Value	DBP *z* Score	*P* Value
EXPT vs CTRL	0.17	0.03	0.19	0.002
Boy vs girl	−0.13	0.09	−0.14	0.01
Heart rate, per 10 bpm	0.20	<0.001	0.15	<0.001
BMI, per kg/m^2	0.07	0.001	0.05	0.001

Data are regression coefficients from multivariable mixed-effects linear regression with examination center as the random variable. BMI indicates body mass index; CTRL, control group (children born at term); DBP, diastolic blood pressure; EXPT, extremely preterm group; SBP, systolic blood pressure.

Table 6. Determinants of SBP and DBP *z* Scores in Relation to Perinatal and Current Characteristics of 6.5-Year-Old Children Born Extremely Preterm (n=171)

	SBP *z* Score	*P* Value	DBP *z* Score	*P* Value
Gestational age, per week	−0.10	0.08	−0.09	0.02
SGA, yes	−0.05	0.75	0.18	0.14
Boy vs girl	−0.07	0.53	−0.12	0.12
BMI, kg/m^2	0.07	0.04	0.02	0.32
Resting heart rate at follow-up, per 10 bpm	0.12	0.01	0.13	<0.001

Data are regression coefficients from a multivariable mixed effects linear regression with exam center as the random variable. BMI indicates body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure. SGA, small for gestational age.

Some limitations exist. We only measured office BPs and not 24-hours ambulatory BP, although the results of such measurements have been similar to those reported in this study.[30,48] We did not record why some invited CTRL candidates declined to participate. Small numbers in some of the subgroup analyses limit our possibility to draw conclusions about the effects of maternal smoking as a potential confounder of the association between preterm birth and later BP. This may affect the generalizability of the results to other countries where maternal smoking in pregnancy is more common than in Sweden. The reason for slightly increased BP remains to be clarified; in particular, genetic and renal factors warrant further investigation.

Perspectives

Six-year-old children who were born extremely preterm have slightly higher BP than their peers born at term. The most obvious clinical implication of our findings is to systematically measure BP at follow-up of older children and young adults who were born extremely preterm. Hypertension at age 30 years increases the lifetime risk of cardiovascular disease by 40%.[36]

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Disclosures

None.

References

1. Beck S, Wojdyla D, Say L, Betran AP, Merialdi M, Requejo JH, Rubens C, Menon R, Van Look PF. The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. *Bull World Health Organ*. 2010;88:31–38.
2. Lawn JE, Blencowe H, Oza S, You D, Lee AC, Waiswa P, Lalli M, Bhutta Z, Barros AJ, Christian P, Mathers C, Cousens SN; Lancet Every Newborn Study G. Every newborn: progress, priorities, and potential beyond survival. *Lancet*. 2014;384:189–205.
3. Group E, Fellman V, Hellstrom-Westas L, Norman M, Westgren M, Kallen K, Lagercrantz H, Marsal K, Serenius F, Wennergren M. One-year survival of extremely preterm infants after active perinatal care in Sweden. *JAMA*. 2009;301:2225–2233.
4. Stoll BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S, Laptook AR, Sanchez PJ, Van Meurs KP, Wyckoff M, Das A, Hale EC, Ball MB, Newman NS, Schibler K, Poindexter BB, Kennedy KA, Cotten CM, Watterberg KL, D'Angio CT, DeMauro SB, Truog WE, Devaskar U, Higgins RD; Eunice Kennedy Shriver National Institute of Child H, Human Development Neonatal Research N. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993–2012. *JAMA*. 2015;314:1039–1051.
5. Moore T, Hennessy EM, Myles J, Johnson SJ, Draper ES, Costeloe KL, Marlow N. Neurological and developmental outcome in extremely preterm children born in England in 1995 and 2006: the EPICure studies. *BMJ*. 2012;345:e7961.
6. Serenius F, Ewald U, Farooqi A, Fellman V, Hafstrom M, Hellgren K, Marsal K, Ohlin A, Olhager E, Stjernqvist K, Stromberg B, Aden U, Kallen K; Extremely Preterm Infants in Sweden Study G. Neurodevelopmental outcomes among extremely preterm infants 6.5 years after active perinatal care in Sweden. *JAMA Pediatr*. 2016;170:954–963.
7. Bonamy AK, Bendito A, Martin H, Andolf E, Sedin G, Norman M. Preterm birth contributes to increased vascular resistance and higher blood pressure in adolescent girls. *Pediatr Res*. 2005;58:845–849.
8. Johansson S, Norman M, Legnevall L, Dalmaz Y, Lagercrantz H, Vanpee M. Increased catecholamines and heart rate in children with low birth weight: perinatal contributions to sympathoadrenal overactivity. *J Intern Med*. 2007;261:480–487.
9. Rakow A, Johansson S, Legnevall L, Sevastik R, Celsi G, Norman M, Vanpee M. Renal volume and function in school-age children born preterm or small for gestational age. *Pediatr Nephrol*. 2008;23:1309–1315.
10. Lewandowski AJ, Augustine D, Lamata P, Davis EF, Lazdam M, Francis J, McCormick K, Wilkinson AR, Singhal A, Lucas A, Smith NP, Neubauer S, Leeson P. Preterm heart in adult life: cardiovascular magnetic resonance reveals distinct differences in left ventricular mass, geometry, and function. *Circulation*. 2013;127:197–206.
11. Kowalski RR, Beare R, Doyle LW, Smolich JJ, Cheung MM; Victorian Infant Collaborative Study G. Elevated blood pressure with reduced left ventricular and aortic dimensions in adolescents born extremely preterm. *J Pediatr*. 2016;172:75–80.e72.
12. Mohlkert LA, Hallberg J, Broberg O, Hellstrom M, Pegelow Halvorsen C, Sjoberg G, Edstedt Bonamy AK, Liuba P, Fellman V, Domellof M, Norman M. Preterm arteries in childhood: dimensions, intima-media thickness and elasticity of the aorta, coronaries and carotids in 6-year-old children born extremely preterm. *Pediatr Res*. 2017;81:299–306. DOI: 10.1038/pr.2016.212.
13. Crump C, Sundquist K, Sundquist J, Winkleby MA. Gestational age at birth and mortality in young adulthood. *JAMA*. 2011;306:1233–1240.
14. Ueda P, Cnattingius S, Stephansson O, Ingelsson E, Ludvigsson JF, Bonamy AK. Cerebrovascular and ischemic heart disease in young adults born preterm: a population-based Swedish cohort study. *Eur J Epidemiol*. 2014;29:253–260.
15. Kaijser M, Bonamy AK, Akre O, Cnattingius S, Granath F, Norman M, Ekbom A. Perinatal risk factors for ischemic heart disease: disentangling the roles of birth weight and preterm birth. *Circulation*. 2008;117:405–410.
16. de Jong F, Monuteaux MC, van Elburg RM, Gillman MW, Belfort MB. Systematic review and meta-analysis of preterm birth and later systolic blood pressure. *Hypertension*. 2012;59:226–234.
17. Hovi P, Vohr B, Ment LR, Doyle LW, McGarvey L, Morrison KM, Evensen KA, van der Pal S, Grunau RE; Collaboration AABPI, Brubakk AM, Andersson S, Saigal S, Kajantie E. Blood pressure in young adults born at very low birth weight: adults born preterm international collaboration. *Hypertension*. 2016;68:880–887.
18. Johansson S, Iliadou A, Bergvall N, Tuvemo T, Norman M, Cnattingius S. Risk of high blood pressure among young men increases with the degree of immaturity at birth. *Circulation*. 2005;112:3430–3436.
19. McEniery CM, Bolton CE, Fawke J, Hennessy E, Stocks J, Wilkinson IB, Cockcroft JR, Marlow N. Cardiovascular consequences of extreme prematurity: the EPICure study. *J Hypertens*. 2011;29:1367–1373.
20. Rysavy MA, Li L, Bell EF, Das A, Hintz SR, Stoll BJ, Vohr BR, Carlo WA, Shankaran S, Walsh MC, Tyson JE, Cotten CM, Smith PB, Murray JC, Colaizy TT, Brumbaugh JE, Higgins RD; Eunice Kennedy Shriver National Institute of Child H, Human Development Neonatal Research N. Between-hospital variation in treatment and outcomes in extremely preterm infants. *N Engl J Med*. 2015;372:1801–1811.

21. Lewandowski AJ, Bradlow WM, Augustine D, Davis EF, Francis J, Singhal A, Lucas A, Neubauer S, McCormick K, Leeson P. Right ventricular systolic dysfunction in young adults born preterm. *Circulation*. 2013;128:713–720.
22. Bonamy AK, Kallen K, Norman M. High blood pressure in 2.5-year-old children born extremely preterm. *Pediatrics*. 2012;129:e1199–e1204.
23. Group E. Incidence of and risk factors for neonatal morbidity after active perinatal care: extremely preterm infants study in SWEDEN (EXPRESS). *Acta Paediatr*. 2010;99:978–992.
24. Haycock GB, Schwartz GJ, Wisotsky DH. Geometric method for measuring body surface area: a height-weight formula validated in infants, children, and adults. *J Pediatr*. 1978;93:62–66.
25. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004;114:555–576.
26. Marsal K, Persson PH, Larsen T, Lilja H, Selbing A, Sultan B. Intrauterine growth curves based on ultrasonically estimated foetal weights. *Acta Paediatr*. 1996;85:843–848.
27. Whincup P, Cook D, Papacosta O, Walker M. Birth weight and blood pressure: cross sectional and longitudinal relations in childhood. *BMJ*. 1995;311:773–776.
28. Chen X, Wang Y. Tracking of blood pressure from childhood to adulthood: a systematic review and meta-regression analysis. *Circulation*. 2008;117:3171–3180.
29. Bracewell MA, Hennessy EM, Wolke D, Marlow N. The EPICure study: growth and blood pressure at 6 years of age following extremely preterm birth. *Arch Dis Child Fetal Neonatal Ed*. 2008;93:F108–F114.
30. Doyle LW, Faber B, Callanan C, Morley R. Blood pressure in late adolescence and very low birth weight. *Pediatrics*. 2003;111:252–257.
31. Hack M, Schluchter M, Cartar L, Rahman M. Blood pressure among very low birth weight (<1.5 kg) young adults. *Pediatr Res*. 2005;58:677–684.
32. Edwards MO, Watkins WJ, Kotecha SJ, Halcox JP, Dunstan FD, Henderson AJ, Kotecha S. Higher systolic blood pressure with normal vascular function measurements in preterm-born children. *Acta Paediatr*. 2014;103:904–912.
33. Crump C, Winkleby MA, Sundquist K, Sundquist J. Risk of hypertension among young adults who were born preterm: a Swedish national study of 636,000 births. *Am J Epidemiol*. 2011;173:797–803.
34. Cook NR, Cohen J, Hebert PR, Taylor JO, Hennekens CH. Implications of small reductions in diastolic blood pressure for primary prevention. *Arch Intern Med*. 1995;155:701–709.
35. Law M, Wald N, Morris J. Lowering blood pressure to prevent myocardial infarction and stroke: a new preventive strategy. *Health Technol Assess*. 2003;7:1–94.
36. Rapsomaniki E, Timmis A, George J, Pujades-Rodriguez M, Shah AD, Denaxas S, White IR, Caulfield MJ, Deanfield JE, Smeeth L, Williams B, Hingorani A, Hemingway H. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. *Lancet*. 2014;383:1899–1911.
37. Keijzer-Veen MG, Finken MJ, Nauta J, Dekker FW, Hille ET, Frolich M, Wit JM, van der Heijden AJ. Is blood pressure increased 19 years after intrauterine growth restriction and preterm birth? A prospective follow-up study in the Netherlands. *Pediatrics*. 2005;116:725–731.
38. Ingelfinger JR. Pediatric antecedents of adult cardiovascular disease—awareness and intervention. *N Engl J Med*. 2004;350:2123–2126.
39. Bonamy AK, Martin H, Jorneskog G, Norman M. Lower skin capillary density, normal endothelial function and higher blood pressure in children born preterm. *J Intern Med*. 2007;262:635–642.
40. Nuyt AM, Alexander BT. Developmental programming and hypertension. *Curr Opin Nephrol Hypertens*. 2009;18:144–152.
41. Cohen G, Vella S, Jeffery H, Lagercrantz H, Katz-Salamon M. Cardiovascular stress hyperreactivity in babies of smokers and in babies born preterm. *Circulation*. 2008;118:1848–1853.
42. Singhal A, Cole TJ, Lucas A. Early nutrition in preterm infants and later blood pressure: two cohorts after randomised trials. *Lancet*. 2001;357:413–419.
43. Elsmen E, Hansen Pupp I, Hellstrom-Westas L. Preterm male infants need more initial respiratory and circulatory support than female infants. *Acta Paediatr*. 2004;93:529–533.
44. Juonala M, Cheung MM, Sabin MA, Burgner D, Skilton MR, Kahonen M, Hutri-Kahonen N, Lehtimaki T, Jula A, Laitinen T, Jokinen E, Taittonen L, Tossavainen P, Viikari JS, Magnussen CG, Raitakari OT. Effect of birth weight on life-course blood pressure levels among children born premature: the Cardiovascular Risk in Young Finns Study. *J Hypertens*. 2015;33:1542–1548.
45. Bonamy AK, Norman M, Kaijser M. Being born too small, too early, or both: does it matter for risk of hypertension in the elderly? *Am J Hypertens*. 2008;21:1107–1110.
46. Dalziel SR, Walker NK, Parag V, Mantell C, Rea HH, Rodgers A, Harding JE. Cardiovascular risk factors after antenatal exposure to betamethasone: 30-year follow-up of a randomised controlled trial. *Lancet*. 2005;365:1856–1862.
47. Krmar RT, Holtback U, Bergh A, Svensson E, Wuhl E. Oscillometric casual blood pressure normative standards for Swedish children using ABPM to exclude casual hypertension. *Am J Hypertens*. 2015;28:459–468.
48. Kistner A, Celsi G, Vanpee M, Jacobson SH. Increased systolic daily ambulatory blood pressure in adult women born preterm. *Pediatr Nephrol*. 2005;20:232–233.

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